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Hydroxyurea and Sodium Phenylbutyrate Therapy in Thalassemia Intermedia

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Hydroxyurea (HU) and sodium phenylbutyrate (SPB) have been shown to increase fetal hemoglobin (Hb F) levels in patients with thalassemia intermedia. The reported effects of these agents in increasing total Hb, however, have been inconsistent and there have been no studies on the combination of these medications. We describe the clinical response, as determined by increases in total Hb and decreased transfusion needs, in five patients with thalassemia intermedia treated with HU alone or in combination with SPB. All of the patients responded with increased levels of Hb F, but the responses in total Hb varied. Of the five patients, two had a marked response in total Hb in excess of 3 g/dl, two responded modestly with an increase in total Hb of 1–2 g/dl, and one did not respond. Prolonged responses were achieved with low doses of HU (3–10 mg/kg/day) and higher doses were associated with mild reversible hematologic or hepatic toxicity and no further increases in Hb. Sodium phenylbutyrate was added to treatment with HU in two patients, but failed to produce an increase in total Hb despite increasing Hb F levels. Of the four patients who responded to HU with an increase in total Hb, all reported symptomatic improvement and three have not required further transfusions. We conclude that low-dose HU therapy in patients with thalassemia intermedia may increase total Hb levels sufficiently to eliminate the need for transfusions. We, therefore, recommend a trial of HU for thalassemia intermedia patients in whom chronic transfusion therapy is being contemplated. Am. J. Hematol. 62:221–227, 1999. © 1999 Wiley-Liss, Inc.

Key words: hydroxyurea; phenylbutyrate; thalassemia; therapy

INTRODUCTION

The β-thalassemias are a genetically heterogeneous group of diseases resulting from decreased β-globin production and a subsequent imbalance in the α/β-globin chain ratio [1]. Excess α-globin chains precipitate within red blood cells (RBC) resulting in hemolysis and ineffective erythropoiesis. Clinically, morbidity arises from severe anemia and extensive compensatory extramedullary hematopoiesis. The phenotypic presentation of the different forms of β-thalassemia varies, but generally correlates with the degree of imbalance in α/β-globin chain synthesis [2]. Enhancing γ-globin chain synthesis within the RBC reduces the α/β-globin chain imbalance and could potentially lead to an improvement in RBC survival and less anemia. Pharmacologic agents that increase γ-globin production, as evidenced by an increase in fetal hemoglobin (Hb F), therefore, become a potential therapy for patients with β-thalassemia. To date, the greatest clinical experience in patients with β-hemoglobinopathies has been with the Hb F modulators, hydroxyurea (HU), and butyric acid [3–12].

Hydroxyurea has long been known to increase Hb F production, although the exact mechanisms of its action are unproven [13]. Trials in patients with sickle cell disease have demonstrated that HU raises fetal hemoglobin levels and results in a substantial reduction in crises in these patients [9,10,14]. In β-thalassemia, a role for HU is much less clear. Several small series have reported

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conflicting results and interpretation of efficacy is complicated by the genetic heterogeneity of the β-thalassemia patients studied [3,4,6,7,12,15,16].

Butyric acid and its derivatives have also been assessed in patients with sickle cell disease and β-thalassemia [17–19]. Butyrate is postulated to augment Hb F by acting at sequences near the transcriptional start site of the γ-globin gene promoter [13,20]. Clinical trials with intravenous arginine butyrate have shown an increase in Hb F production, but inconsistent responses in increasing total Hb [18,19]. Sodium phenylbutyrate (SPB), an oral derivative of butyric acid, has also been used in patients with sickle cell disease and β-thalassemia [8,17]. In β-thalassemia, response was limited to patients who were not transfusion-dependent (thalassemia intermedia) and, again, was not predictable [8].

In general, the greatest responses to both HU and butyrate have been in patients with β-thalassemia intermedia and may reflect underlying genetic influences which allow them to produce more hemoglobin in the first place. Thalassemia intermedia, while not strictly transfusion-dependent, is still characterized by significant morbidity [1]. Because these patients are not regularly transfused, they are particularly susceptible to the effect of extramedullary hematopoiesis, including splenomegaly, growth and pubertal delay, and osteoporosis. In addition, thalassemia intermedia patients frequently become iron overloaded from increased gastrointestinal absorption and periodic transfusions. The hemoglobin of these patients frequently hovers at a compromising level and the decision to begin regular transfusions is often a balance between the complications of extramedullary hematopoiesis and transfusional iron overload. Because they are not transfusion-dependent and even a modest increase in total Hb may reduce extramedullary hematopoiesis, patients with thalassemia intermedia become attractive candidates for Hb F modulators such as HU and butyrate.

We have adopted a policy of offering our thalassemia intermedia patients who suffer from severe anemia, or the effects of extramedullary hematopoiesis, a trial with HU and/or sodium phenylbutyrate in an attempt to avoid transfusion therapy. Despite considerable information on the effects of these medications on γ-globin and Hb F production, there is little information on the *clinical* response of thalassemia intermedia patients treated with HU or butyrate. In addition, there has been only one report on two siblings treated with the combination of these two medications [23]. In this report, we describe the hematologic and clinical responses of 5 patients with thalassemia intermedia treated with low-dose hydroxyurea alone or in combination with sodium phenylbutyrate.

TABLE I. Thalassemia Intermedia Patient Characteristics

Patient	Age (years)	Sex	Ethnicity	Thalassemia mutation
1	42	M	Vietnamese	[41/42(−TCTT)&E]
2	43	M	Cambodian	IVS II-654&E
3	34	F	Chinese	homozygous −28(A-G) β+
4	7	M	Laotian	[41/42(−TCTT)&E]
5	2	M	Filipino	homozygous 45 kb deletion

METHODS

Patients

Five patients with thalassemia intermedia (Table I) were treated with HU alone, or in combination with SPB. The study protocol was approved by the Children's Hospital Oakland Investigational Review Board, and informed consent was obtained from all participants. A detailed medical history and physical exam were obtained upon entry into the study.

Study Protocol

All 5 patients were treated with hydroxyurea. The starting dose was between 3 and 10 mg/kg/day given orally once a day. In general, the dose of HU was adjusted upward in increments of 2–5 mg/kg/day at 8-week intervals until toxicity developed. Hematological toxicity was defined by an absolute neutrophil count (ANC) $<1{,}500/mm^3$, an absolute reticulocyte count (ARC) $<80{,}000\ mm^3$, or a platelet count $<80{,}000/mm^3$. Hepatic and renal toxicity were defined by a 2-fold increase in serum glutamate pyruvate transaminate SGPT or a >50% increase in serum creatinine concentration. If toxicity occurred, treatment was stopped until blood counts returned to normal and then resumed at the same dose. If toxicity occurred a second time at the same dose, then the dose was lowered, and, if tolerated, this was considered the maximum tolerated dose (MTD). Once the MTD was reached, oral sodium phenylbutyrate (SPB) was started in two of the patients at 10 g/m^2/day divided into three doses.

Laboratory and Clinical Monitoring

Before commencing HU, all patients underwent laboratory testing including a complete blood count with differential, reticulocyte count, serum chemistries, ferritin, serum iron, total iron binding capacity (TIBC), erythropoietin level, urinalysis, and pregnancy testing. Viral testing including studies for hepatitis A, B, and C, as well as human immunodeficiency virus was performed. Quantitative hemoglobin electrophoresis was obtained prior to treatment. Baseline total Hb and Hb F were calculated as an average of 3–4 values immediately preceding the initiation of HU. If the patient had received a transfusion within 2 months of initiating HU, then the baseline Hb level was determined from the most recent untransfused

TABLE II. Hematologic Changes in Thalassemia Intermedia Patients Treated With Hydroxyurea and Sodium Phenylbutyrate*

		Patient				
		#1	#2	#3	#4	#5
Baseline	Hb (g/dL)	8.1	7.1	7.1	6.5	5.6
	Hb F (%)	32	33	18	35	100
	MCV (fl)	80	56	66	65	87
	MCH (pg)	25	20	20	20	25
	NRBC (#/100 WBC)	490	395	700	35	390
HU alone	Hb (g/dL)	11.5	7.7	8.8	7.8	9.6
	Hb F (%)	58	39	38	50	100
	MCV (fl)	92	67	91	71	96
	MCH (pg)	30	20	27	22	30
	NRBC (#/100 WBC)	175	200	360	12	250
HU and SPB	Hb (g/dL)	11.3	7.8	–	–	–
	Hb F (%)	62	53	–	–	–
	MCV (fl)	90	80	–	–	–
	MCH (pg)	31	21	–	–	–
	NRBC (#/100 WBC)	175	220	–	–	–

*Hb = hemoglobin, Hb F = fetal hemoglobin, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, NRBC = nucleated red blood cell, HU = hydroxyurea, SPB = sodium phenylbutyrate, baseline = average value immediately preceding HU or most recent untransfused value.

value. All patients were treated with folate supplementation for at least 6 months prior to initiating HU and continued on folate throughout HU therapy.

During treatment, all 5 patients were monitored for clinical side effects and compliance with dosing. Complete blood count with reticulocyte count was performed every 2 weeks and a chemistry panel obtained every 4 weeks until the MTD was reached. Thereafter, these labs were checked monthly. Ferritin, TIBC, and serum iron were determined at 6-month intervals. Hemoglobin electrophoresis including determination of Hb F, Hb E, and Hb A_2 was performed throughout HU and SPB therapy. Hb F was measured using the alkaline denaturation technique and quantified by spectrophotometry [21]. Hb A_2 was measured using ion exchange chromatography and spectrophotometry.

RESULTS

Patient 1 is a 42 year-old Vietnamese male with Hb E β−thalassemia [41/42(-TCTT)& E] who was first diagnosed in a Thai refugee camp at age 25 years when he developed spastic paresis of the left leg due to spinal cord compression from extramedullary hematopoiesis. He received spinal irradiation and his first RBC transfusion to reduce extramedullary hematopoiesis. Upon arrival to the United States at age 29 years, the patient presented with a baseline Hb of 8.1 g/dl and persistent spastic hemiparesis with progressive urinary incontinence. The patient received a second course of low-dose irradiation, followed by regular RBC transfusions to maintain a Hb greater than 12 gm/dl. Massive splenomegaly was exacerbated by this period of regular transfusions, necessitating splenectomy. With continued transfusions, the patient developed transfusional iron overload with ferritin levels as high as 8000 ng/dl and marked iron overload documented by liver biopsy. The patient subsequently developed bilateral sensorineural high frequency hearing loss as a result of high-dose desferal. On a program of intermittent transfusion, the patient again developed evidence of progressive extramedullary hematopoiesis with bilateral paraspinous masses.

During the year preceding the initiation of hydroxyurea, the patient required 75 cc/kg/year of packed RBCs. Immediately before starting HU, the patient's Hb was 9.7 g/dl with a Hb F of 3.1 g/dl (32%) 4 weeks after receiving a transfusion (Table II, Fig. 1). The patient's initial HU dose of 7.5 mg/kg/day was increased to 15 mg/kg/day at week 14 with a rise in Hb to 11 g/dl by week 20. During HU therapy, the patient's Hb F increased to a maximum of 6.7 g/dl (62%). He maintained a steady-state Hb level of 10.9–11.5 g/dl, without further need for transfusions during this period. After 36 weeks of HU therapy, the patient's dose was reduced to 7.5 mg/kg/day because of elevated liver transaminases (SGPT = 110 U/l). The transaminases normalized on this dose, and the patient was begun on sodium phenylbutyrate (SPB). The total Hb level did not change with the addition of SPB, despite an increase in Hb F to 7.0 g/dl (64%). During therapy with SPB, the patient complained of nausea, epigastric pain, and progressive fatigue. After 16 weeks of combined HU and SPB treatment, SPB was discontinued. The patient's Hb F subsequently fell to 5.8 g/dl (51%) after elimination of SPB, but his total Hb level

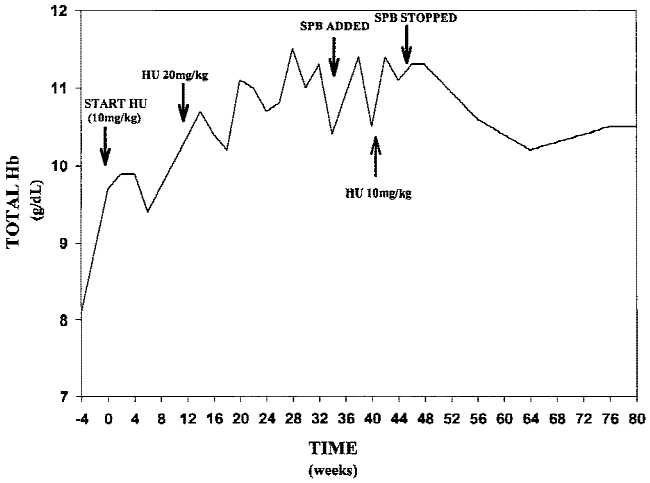

Fig. 1. Hemoglobin changes in a thalassemia intermedia patient treated with hydroxyurea and sodium phenylbutyrate. Hydroxyurea (HU) was initially started alone and sodium phenylbutyrate (SPB) was later added to HU therapy. Week −4 = most recent untransfused (baseline) Hb; week 0 = hemoglobin at start of HU therapy, 4 weeks after last transfusion.

remained at 11.3 g/dl. He has continued on this dose of HU for a total of 2 years with a stable Hb. Throughout therapy with HU and SPB, the patient continued chelation with subcutaneous desferal. The patient no longer requires chelation therapy and remains off of transfusions.

Patient 2 is a 43-year-old Cambodian male with Hb E β-thalassemia (IVS II-654 & E) who required his first RBC transfusion at age 30 years for a Hb of 5.9 g/dl. Upon arrival to the United States at age 31 years, the patient presented with a baseline Hb of 7.1 g/dl, massive splenomegaly, fatigue with mild exertion, and anorexia. Splenectomy resulted in temporary improvement in the patient's symptoms with a transient increase in Hb to 8.0 g/dl. Subsequent fatigue and lightheadedness severely limited his daily functioning and ability to work. When paraspinous masses were detected on chest radiography, a chronic transfusion regimen was initiated. Viral studies for hepatitis C were positive, and a liver biopsy revealed marked hemosiderosis (liver Fe = 26.5 mg/g dry liver weight), chronic active hepatitis, and cirrhosis. Prior to beginning HU therapy, the patient had received 40 cc/kg/yr of packed RBCs. Upon initiation of HU therapy, the patient had a Hb of 7.3 g/dl with a Hb F of 2.4 g/dl (33%). He was started on an initial HU dose of 7.6 mg/kg/day with a dose escalation to 15 mg/kg/day after 8 weeks. Despite an increase in MCV from 56 to 71 fl, his total Hb averaged only 7.7 g/dl throughout therapy with HU. The Hb F increased to only 3.0 g/dl (39%). Sodium phenylbutyrate was added to his HU therapy at 26 weeks resulting in a peak in Hb F of 4.1 g/dl (53%) by 12 weeks of combined therapy. Unfortunately, this modest increase in Hb F had no effect on the patient's total Hb. SPB was thus discontinued and an attempt to increase total Hb by decreasing HU to 7.6 mg/kg/day failed to produce a response. Because of the lack of response to HU, along with the development of chronic leg ulcers and hepatitis C-induced liver failure, HU was discontinued and the patient referred for liver transplantation.

Patient 3 is a 34-year-old Chinese female with β-thalassemia intermedia [homozygous -28(A-G) β+]. After the birth of her second child at age 24 years, she received intermittent transfusions for fatigue. She eventually presented with severe anemia (Hb = 6.8 g/dl), extreme fatigue and massive splenomegaly. A splenectomy temporarily stabilized her Hb at 7.6 g/dl, but, symptomatically, she continued to decline with Hb levels averaging 7.1 g/dl. She received a 3-week trial of intravenous arginine butyrate which increased her Hb F but produced no change in her total Hb (baseline Hb = 7.1 g/dl). Because of persistent symptomatic anemia, the patient began a regular transfusion program and chelation with desferal. Recurrent tinnitus and high-frequency hearing loss resulted in multiple interruptions in desferal chelation. The patient required 150 cc/kg/yr of PRBCs to maintain her Hb greater than 9 g/dl. Mild osteoporosis and evidence of hypogonadism resulting from chronic iron overload were subsequently diagnosed. The patient began HU immediately after a transfusion for a Hb = 7.1 g/dl (Fig. 2). She was initially started on HU at 10 mg/kg/day and this dose was increased to 14.7 mg/kg/day coincident with a peak in Hb to 9.3 g/dl. By 16 weeks, the Hb remained at 9.0 g/dl and the dose was further increased to 20 mg/kg/day. This resulted in a drop in the ANC which failed to return to baseline until the HU dose was incrementally lowered back to 10 mg/kg/d. On this dose, her Hb was 8.8 g/dl and Hb F levels climbed from 1.3 g/dl (18%) to 3.3 g/dl (38%) by 34 weeks of therapy. After 36 weeks, HU was temporarily discontinued to determine whether cessation of HU would result in a return to pretreatment levels of Hb. After 14 weeks off of HU, the patient's total Hb and Hb F dropped to 7.1 and 1.6 g/dl (23%), respectively. HU was resumed with a return in total Hb to 8.6 g/dl and Hb F to 2.2 g/dl (26%). She has remained on HU therapy with a stable Hb and has not required a transfusion in over 3 years.

Patient 4 is a 7-year-old Laotian-American male with HgbE β-thalassemia (41/42(-TCTT)&E) who remained free of thalassemia complications during his infancy and toddler years. He subsequently developed progressive splenomegaly [7–8 cm below the left costal margin (LCM)] by the age of 4 years. He also developed profound maxillary hyperplasia with concurrent micrognathia and obstructive sleep apnea. His baseline Hb averaged 6.5 g/dl in the year prior to treatment with HU. At the time HU was started, his Hb was 6.8 g/dl and Hb F was 2.4 g/dl (35%). At an initial dose of 10 mg/kg/d, a

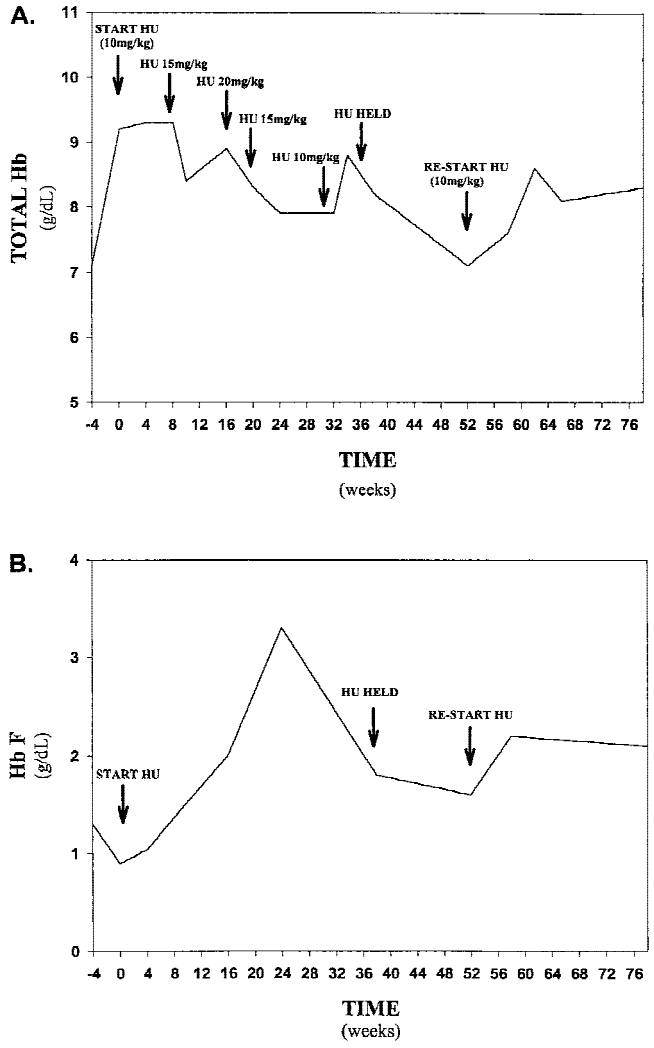

Fig. 2. Total hemoglobin (Hb) and fetal Hb (Hb F) changes in a thalassemia intermedia patient treated with hydroxyurea (HU). (A) Total Hb levels with dose adjustments in HU. (B) Hb F levels throughout treatment with HU demonstrating lack of correlation with total Hb levels. Week −4 = most recent untransfused (baseline) Hb; week 0 = hemoglobin at start of HU therapy, immediately after last transfusion.

striking reduction in spleen size from 7 cm to 4.5 cm below the LCM was noted after 8 weeks of therapy. The patient's Hb increased modestly to 7.8 g/dl, and Hb F rose to 3.9 g/dl (50%). Several attempts at dose increases resulted in mild neutropenia and thrombocytopenia. HU was discontinued to confirm that the increase in Hb was indeed due to HU. After only 5 weeks off of HU, the total Hb dropped to 6.7 g/dl and the patient's spleen had doubled in size. The patient's Hb F, however, remained elevated at 3.4 g/dl (51%). Hydroxyurea was reinitiated at a dose of 12 mg/kg/day with a return in Hb to 7.6 g/dl and HbF to 3.8 g/dl (50%). Spleen size again decreased to 4 cm below LCM. After 72 weeks of HU therapy, the patient was hospitalized with bilateral pneumonia and a Hb of 5.4 g/dl, necessitating transfusion. A decision to continue regular transfusions was subsequently made by the patient's mother.

Patient 5 is a 2 ½-year-old Filipino male with thalassemia intermedia (homozygous 45 kb deletion) definitively diagnosed at 1 year of age at which time he was asymptomatic. At 15 months of age, the patient required his first transfusion for worsening anemia (baseline Hb = 5.6 g/dl) and progressive splenomegaly associated with a febrile illness. After this first transfusion, the patient's Hb dropped from 8.5 g/dl post-transfusion to 6.3 g/dl; the child was transfused a second time and again experienced a precipitous drop in Hb from 10.7 to 5.2 g/dl. A workup for a transfusion reaction revealed a warm autoantibody. A third transfusion resulted in another episode of severe autoimmune hemolytic anemia. The patient was treated with high-dose steroids and erythropoietin, along with HU at a dose of 5 mg/kg/day when his Hb decreased to 4.0 g/dl. He ultimately required a splenectomy to manage his autoimmune hemolytic anemia. Post-splenectomy, his Hb recovered to 9.0 g/dl, HU was discontinued, and prednisone was tapered. The total Hb peaked at 10.2 g/dl but declined to 7.5g/dl after 10 weeks off of all therapy. Hydroxyurea was restarted at a dose of 3 mg/kg/day, but the patient's Hb continued to decline to 5.8 g/dl with an admission for fever and a presumed viral infection. A Coombs tests at that time revealed a mild warm autoantibody with a negative indirect Coombs test and the patient was transfused. Post-transfusion, Coombs testing again became positive and the patient's Hb dropped from a high of 11.4 to 6.1 g/dl within 1 week. High-dose prednisone was reinstituted along with HU, and the patient received 2 doses of intravenous immune globulin. After a gradual steroid taper and discontinuation of immune globulin, the patient's Hb rose steadily from 6.4 to 9.6 g/dl after 10 weeks on HU alone. Coombs testing is now negative and the patient has not required transfusions in over 8 months.

DISCUSSION

Early reports of the use of fetal Hb modulators such as HU and butyric acid compounds have been promising, but investigations to date have generally focused on laboratory changes such as γ-globin and Hb F production [10,16,18,19], rather than on the clinical impact from the use of these medications. We report here the results of treating five patients with thalassemia intermedia in an attempt to avoid the morbidity of transfusions and subsequent iron overload. The effects on total Hb and the need for further transfusions were, therefore, the primary measure of efficacy. Like previous studies evaluating laboratory responses, we found that clinical response was highly variable [4,10,12,18]. Moreover, a clinical response did not always correlate with an increase in fetal

Hb production. Although all patients demonstrated an increase in Hb F with treatment, the concomitant rise in total Hb was not predictable. Two patients had increases in Hb in excess of 3 g/dl, two responded modestly with a 1–2 g/dl increase, while the last patient showed little change. Other reports have conflicted in this regard. A few small studies have reported a correlation between increased Hb F and total Hb while others have shown that some patients with increased Hb F have no response in total Hb after treatment with HU [4,15,16]. This suggests that HU may act in a nonselective manner and effect more than γ-globin production alone. Indeed, one study demonstrated that HU can result in increases in α-, β-, and γ-globin levels [12]. It may be that the sum of the effects on globin production is more important than simply γ-globin production. Furthermore, the relative increases in individual globins may be influenced by other genetic modifiers, in addition to the particular β-globin genetic defect.

In our study, four of the five patients treated with HU were able to avoid or postpone the need for transfusions. This contrasts to other studies in which there were, in general, few responders [6,16]. A possible explanation for our success is that lower doses of HU were used. None of our patients had an improved response with escalation of the HU dose. In fact, most of the patients showed a decrease in Hb when the dose of HU was increased. In other studies, the dose was escalated in the absence of severe myelosuppression, potentially abolishing any effect that might have been apparent had HU not been increased. Hajjar et al. reported the occurrence of tachyphylaxis with time in three thalassemia intermedia patients treated with HU [6]. It is possible that what this group attributed to tachyphylaxis actually reflected the effect of dose escalation. None of our patients showed a decrease in response with time, despite up to 3 years of therapy with HU. A report by McDonaugh supports this hypothesis with a summary of a patient whose Hb decreased with increasing doses of HU [22]. Furthermore, responses have been demonstrated with doses as low as 3 mg/kg/day which is one-third of the starting dose used in many of the reports documenting little or no benefit [12].

Hydroxyurea was easy to use and was well-tolerated in our patients. With the exception of mild reversible myelosuppression and elevation in liver transaminases with doses greater than 10 mg/kg/day, HU had no short-term toxicity. Responses to therapy occurred within 8–12 weeks of starting HU, making dose escalations potentially unnecessary. Given the ease of therapy and lack of toxicity, a brief trial of HU in patients with thalassemia intermedia may be warranted to identify those patients who will benefit from HU. The long-term risks from a brief trial of HU are likely to be minimal for those patients who do not respond. For those patients who do respond, the complications associated with chronic transfusion can be prevented. Hydroxyurea therapy may be particularly advantageous in children, allowing for normal growth and achievement of sexual maturity without the need for transfusions.

In contrast to HU, SPB was of no clinical benefit in the two patients treated with a combination of HU and SPB. Except for a letter to the editor describing treatment in two siblings, there are no publications on the use of the combination of these medications in thalassemia [23]. However, one study investigating the combination of these medications in sickle cell disease suggested that combination therapy may have an additive effect on Hb F production [24]. Both of our patients showed increases in Hb F when SPB was added to HU, but neither patient responded with an increase in total Hb. Therapy with SPB alone has been reported to increase total Hb and Hb F in patients with thalassemia intermedia, and it is unclear why our patients failed to show an increase in total Hb, despite an increase in Hb F [8]. Therapy with SPB is very difficult as adult patients must ingest 35–40 tablets per day, resulting in significant dyspepsia. These discouraging results may limit its potential, however, other doses or schedules of administration may improve response to butyrate [25]. Also, other short chain fatty acids have been shown to produce an increase in Hb F and may prove useful alone or in combination with HU [26].

CONCLUSION

In summary, of the 5 patients with thalassemia intermedia treated with HU, 4 had a sufficient response to avoid further transfusions. This was accomplished with minimal, reversible toxicity and low doses of HU. The addition of sodium phenylbutyrate did not result in any further clinical improvement. We, therefore, recommend a trial of HU in thalassemia intermedia patients in order to minimize the need for regular transfusions and concomitant iron overload.

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